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LIBER, STOCKHOLM 1987

Description

Background of the Invention

Field: This disclosure is concerned generally with intravenous nutrition and specifically with the use of lipid combinations which, on hydrolysis, yield controlled amounts of both long and medium chain fatty acids.

Prior Art: Among the most important goals of nutritional support during severe injury or sepsis are a reduction in net protein catabolism and an increase in protein synthesis, especially in those tissues concerned with wound healing and host defense mechanisms.

Usually during severe stress, regardless of the initiating cause, there is an important mobilization of amino nitrogen from skeletal muscle and connective tissue to support the synthesis of visceral and acute phase secretory proteins. This metabolic response results in the acceleration of protein degradation and an elevation of energy expenditure or, as used herein, hypercatabolism. In addition, muscle protein catabolism provides the precursors for oxidation of branched chain amino acids and the synthesis and release of alanine for hepatic metabolism as a gluconeogenic substrate. Urinary nitrogen excretion is often elevated and the organism suffers negative nitrogen balance. If the stress is persistent, the nitrogen losses will eventually deplete the body's protein pool and this hypercatabolism will compromise criticel functions resulting in a progressive deterioration of lean body mass and multiple organ failure. There is no doubt about the importance of dietary amino acid administration during severe injury. But beceuse of the close relationship between protein and energy matabolism, calorie intake can also modify the utilization of emino acids, apare nitrogen and support protein synthesis.

The sources of non-protein calories commonly used in total parenteral nutrition sre dextrose aolutions and long chain fatty acid triglycerlde (LCT) emulsiona composed of either soybean or safflower oil: However, there ia increasing concern about the undesirable effects of excessive dextroae administration in critically ill patiants. Inaulin realatance limita glucose oxidatlon and promotea lipid bioaynthesia increasing the productlon of CO_2 and the risks of developing fatty liver. On the other hand some controversy persists concerning the utilization of long chain fatty acids during aevere stresa. Some investlgators heve suggested that the nitrogen sparing capacity of long chain triglyceride emulsiona are due solely to the glycerol that the emulaions contain. In severe streas long chain fatty acids mey have a reduced capacity to enter tha mictochondria for β-oxidation, aome inveatigators have reported s reduction in muscle carnitine levels which asaista thalr entry into the mitochondria.

In addition, intravenous diets in which long chain triglyceride emulsions contributa over 50% of nonprotain calorie intake have been asaociated with anergy to cutaneoua antigena and T-lymphocyte dyafunction. Furthermore, critically ill patienta receiving such diets ere at Increesed risk of developping aecondary complications.

Thesa considerations have promoted the aearch for nonconventional energy aourcea that can be more essily utilized in injury. Medium chain triglycarides (MCT) formed from saturated fatty acids with chain lengths of 6 · 14 carbona hava a unique metabolism that may be of importance during injury. They are metabolized more rapldly than long chain triglyceridaa because they do not require carnitine to enter into the mltochondria whera they are used for β-oxidatlon. Moreover, the depositlon as fat is less during medium chain triglyceride infusions than during long chain triglyceride administration because they require an Initial elongation to 16 - 18 carbon length chains. Their repid utilizstion as an energy substrete and frequent generation of ketone bodies may represent an important mechanism to spere nitrogen and support protein synthesia during injury. Proposed enteral and parenteral applications for MCTs have been described by A. C. Bach and V. K. Babayan in "Medium-Chain Triglycerides:an Update", Am. J. Clin. Nutrition 36, pp. 950 - 962, November, 1982. Parenteral applicatlons of MCT/LCT mixtures have been described by D. Sailer snd M. Müller in "Medium Chain Triglycerides in Parenteral Nutrition", J. Parent. and Ent. Nutr., Vol. 5, No. 2, pp. 115 - 119 (1981). Toxicity to intravenous administration of large quantities of MCT has been reported. Intravenous administration in dogs has produced somnolence, vomiting, coma and death. Similar findings have slso been observed in fed, but not fasted rats. The effects of such nutrition on the hypercatabolic mammal, however, have not been investigated in great detail to date. As used herein, the term hypercatabolic refers to a state of elevated energy expenditure in a mammal which, if uncorrected, results in detrimental protein catabolism. Such state may be caused by a variety of life-threatening conditions including surgical injury, trauma, infection and the like.

As disclosed below, we have examined various calorie sources for total parenteral nutrition (TPN) in burned rats. We have examined the significance of infusing in addition to a basal intake of dextrose and amino acids, 33% more calories as either dextrose or a commercially available long chain triglyceride emulsion (soybean oil), medium chain triglyceride emulsion or a structured lipid emulsion composed of 60% medium chain and 40% long chain triglycerides. We evaluated the effect of these diets on changes in body weight, nitrogen balance, liver nitrogen, serum glucose, β-hydroxybutyrate, lactate and albumin concentrations. Whole body leucine kinetics and protein fractional synthetic rate in muscle and liver were determined by using a constant intravenous infusion of L-[1-^{14}C]leucine as a tracer. Quite surprisingly, we found that when certain lipid sources were inclüded in the TPN studies, the mammals studies were significantly more anabolic than animals receiving the other intravenous diets. As measured by nitrogen and net leucine balance, rats infused with one of our controlled lipid sources were in significant positive balance. Using the same controlled lipid, the highest hepatic protein synthesis was obtained and, in addition, it was found that more than 60% of the test animals'

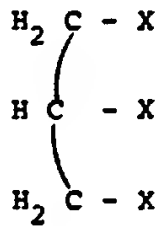
total caloric requirements could be satisfied with that lipid source without impairment of the function of the animal's reticuloendothelial system (RES). Details of the controlled lipid sources and their uses are described below.

Brief Description of Figures

Figure 1 is a graph comparing % body weight change with various I.V. nutritional supports disclosed herein.
Figure 2 is a graph showing cumulative nitrogen balance with the same various I.V. nutritional supports.

Summary of the Invention

We have found that it is possible to enhance protein anabolism in an hypercatabolic mammal by parenterally edministering to the mammal nutritionally sufficient sourcee for amino acids, carbohydrates and lipids, the lipids themselves comprising a controlled source of triglycerides which, on hydrolysis, yields both long chain fatty acids and medium chain fatty acids, preferably about 20 to 80% long chain fatty acids and about 80 to 20% medium chein fetty acids. The controlled source of triglycerides is cepable of providing more than 60% of the hypercatabolic mammels caloric requirements without impeirment of the RES of the mammal. In one embodiment the lipids comprise e mixture of synthetic triglycerides (or structured lipids) having the formule



where X represents long end medium chain fatty ecid residues with at least one of eech being present. Preferebly, a long chain fatty acid residue is an essential fatty ecid residue and e medium chain fatty acid residue is selected from C_8, C_{10}, and C_{12} aatureted fatty acid residues. In another (less preferred) embodiment, the lipids comprise e physicel mixture of long chain triglycerides and medium chain triglycerides.

Specific Embodiments

MATERIAL AND METHODS

Animals end Experimental Design

Male Spraque-Dawley rats (Cherles River Breeding Laboratories, Wilmington, MA) were maintained in individual cages in a light-controlled room at a temperature of 26 - 28° C. During one week prior to study they were fed a stock leboratory diet (Charles River D-3000, Agwey Agriculturel Products, Minneapolis, MN) and tap water and libitum. After that period, under sodium pentobarbital anesthesis (25 mg/kg body wt), 35 rats weighing between 215 - 265 g underwent insertion of a 0.020" x 0.037" (0.5 x 0.94mm) Silastic® catheter (Dow Corning Labs., Corning, NY) through the external juguler vein into the superior vene ceva as has been described. The catheter was attached to a flow-through swivel (Instech Lab., Philadelphia, PA) that allowed a continuous infusion and free movement by the rets. At the same time the animals received a full thickness scald burn injury by immersing 25% of their body surfece erea in boiling water for 15 seconds. Following one day of recovery with intravenous infusion of 0.9% sodium chloride the rats were randomly assigned to five groups of seven animals each to receive totel parenteral nutrition using a Holter peristaltic pump (Holter #903, Extracorporeal Co., King of Prussia, PA) for three deys. All enimels received isovolemic solutions (31 ml/100 g body weight) containing 3.68% emino acids (Aminosyn, Abbott Laboratories, North Chicago, ILL), 14.6% dextrose, electrolytes, trece elements end vitemins that delivered 11.4 g emino acid/kg BW. day and 200 kcals/kg BW. day (Table 1).

Table 1

Electrolyte, Trace Element and Vitamin Content of the Total Parenteral Nutrition Solutions

Electrolytes	(g/liter)
Sodium Chloride	1.19
Sodium acetate	1.67
Potassium chloride	1.52
Potassium phosphate	1.06
Potassium acetate	1.00
Magnesium sulfate	0.99
Calcium gluconate	1.25

Trace Elements	(mg/liter)
Chromium chloride ($CrCl_3 \cdot 6H_2O$)	0.2
Zinc chloride	21.2
Cupric chloride ($CuCl_2 \cdot 2H_2O$)	9.1
Mangenese chloride ($MnCl_2 \cdot 4H_2O$)	4.9
Sodium iodide	0.2

Vitamins	(per liter)
Ascorbic acid	68 mg
Retinol	2230 IU
Ergocalciferol	135 IU
Thiamine	2.0 mg
Riboflavin	2.4 mg
Pyridoxine	2.7 mg
Niacin (as an amide)	27.1 mg
Dexapanthenol	10.2 mg
Di-alphatocopherol	10.2 mg
Biotin	40.6 ug
Folate	0.3 mg
Cyanocobalamin	3.4 ug
Choline chloride	203 mg

To Group I no additional calories were given. Groups II, III, IV and V received an additional 100 calories/kg BW.day as either dextrose (Group II); a soybean oil lipid emulsion (Intralipid®), (Group III); a medium chain triglyceride emulsion composed of 75% capric acid (C8:0) and 25% caprylic acid (C10:0) (oil obtained from Capital City Products, Columbus, OH) (Group IV); or a chemically structured lipid emulsion composed of triglycerides synthesized from 40% safflower oil and 60% medium chain triglycerides (Captex 810 B, Capital City Products). The Captex 810 B product is a synthetic fat also referred to as a structurad lipid. The preparation and use of such structured lipids is described in U.S. Patent No. 3,450,819 to V. Babayan et al.

All of the lipid emulsions were provided by Cutter Laboratories, Berkeley, CA. The composition of the administered nutrients is presented in Table 2.

Table 2

Dietary Intake in the Experimental Groups

	Total Calorie Intake (kcal/kg·day)	Protein Intake (gAA/kg·d)	Calorie:N Ratio	Nonprotein Calories % Dextrose	% Lipid
Group I (AA + low Dextrose)	200	11.4	110:1	100	0
Group II (AA + high Dextrose)	300	11.4	165:1	100	0
Group III (AA, Dextrose + LCT emulsion)	300	11.4	165:1	65	35
Group IV (AA, Dextrose + MCT emulsion)	300	11.4	165:1	65	35
Group V (AA, Dextrose + Structured Lipid)	300	11.4	165:1	65	35

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The animals were reweighed at the beginning and after three days of total parenteral nutrition- Total urinary excretion was collected daily.

During the last 3.5 hours of parenterel nutrition support, the rets were housed in closed metabolic chambers that allowed the collection of the expired breath. At this time, a tracer amount of L-[1-^{14}C] leucine (New England Nuclear Laboratories, Boston, MA) was added to nutrient solutions so that 1 µCi/hour was infused. [^{14}C] Radioactivity in the expired breath and total carbon dioxide production were measured hourly. At the end of the isotope infusion, the rets were killed by decapitation and arterial-venous blood from the neck was drained into chilled empty and hepaninized tubes. The blood samples were centrifuged and 0.5 ml of serum was deproteinized with equal emounts of 30% perchloric acid for glucose, β-hydroxybutyrate and lactate measurements. Immedietely after the blood collection the whole liver was weighed, a sample was stored in normal saline solutions for nitrogen analysis and a piece of gastrocnemius muscle was homogenized in 5 ml of ice-cold 10% sulphosalicylic acid and stored at -30° C.

Analytical Methods

Daily nitrogen balances were calculated besed on the total urinary nitrogen excretion. Total urine nitrogen as well as total liver nitrogen were determined using spectrophotometric enalysis (Autoanalyzer, Technicon Instrument Co., Tarryton, NY) following a micro-Kjeldahl digestion (Technicon Block Digestor).

Glucose, β-hydroxybutyrate and lactate levels were determined on the deprotainized serum by enzymatic methods. Serum insulin was datermined by a double isotope radioimmunoassay and serum albumin by bromocreosol green colorimetry.

During the constent infusion of L-[1-^{14}C]leucine, room air was circuleted through the chambers at a rata of 1.6 L/min and the [^{14}C] labeled cerbon dioxide appearence in the expired breath wea trapped in scintillation vials containing hyamine hydroxide (Packerd Instrument Co., Downera Grove, ILL) and meesured with a Beckman LS-8000 liquid scintillation spectrometer (Beckman Instruments, Fullerton, CA) as described. The total CO_2 production was measured by trapping timed collections of expired breeth in berlum hydroxide (ASCARITE II®, A.H. Thomas & Co., Philadelphie, PA).

Plaama amino acid concentrations were determined on the supernatent of 1 ml of plasma treated with 0.2 ml of 30% sulphosalicylic acid and separated by centrifugetion using e D-400 Amino Acid Analyzer (Dionex Corporation, Sunnyvale, CA). Free leucine specific redioectivity was determined as previously described. Plasma ketoisocaproate (KIC) waa eluted off a ^{C}18-reverse phaae 10u Bondapak column (Weters Asaociates, Medfield, MA) using a 95% phosphate buffer, 5% acetonitrile solution at 0.9 mla/min. The KIC was detected at 210 nm and the peeks were manually collected for liquid scintillation apectrometry.

Total [^{14}C] redioectivity of plesme and infusete wes measured using a commercial acintillant (Monofluor, Nationel Diagnostic Inc., Somerville, NJ). Efficiency of counting (between 65 - 75%) was calculatad with external atandards and all samples were counted to e standard error of less than 2.5%.

The muscle preclpitates were washed 3 times with 2% sulphosalicylic acid end after being dried they were solubillzed in quetemery ammonium hydroxide (Soluene-350, Packard Co.) to be counted in a commerciel scintillant (Batafluor; Netionel Diagnostic Inc., Sommerville, NJ) and spectrophotometrically analyzed for total nitrogen following micro-Kjeldahl digestion.

Calculations

Rates of whole body leucine appearance have been estimated from the equation:

$Q = I/Sp\ max$

where Q (Flux) is the amount of leucine entering end leaving the plasma pool in µmol - h^{-1}; I is the isotopic intravenous infusion rate in dpm - h^{-1}; and Sp max is the specific radioactivity of plasma free L-leucine at the end of the 3.5 h infusion. It was assumed a plateau labeling (steady state) of the plesma compartment was achieved when it was reached in the expired breath (between 2 - 3.5 h of continuous L-[1-^{14}C] leucine infusion).

The percentage of flux oxidized was derived from the [^{14}C] carbon dioxide in the expired breath (estimating that 10% did not appear in the breath) in dpm, the hourly production of CO_2 and the known infusion rate of the tracer (I). The oxidation rate of leucine was then calculated by multiplying the flux (Q) by the percentage oxidized.

The incorporation of leucine into whole body protein was subsequently derived from the difference between leucine flux and oxidation and the leucine release from protein breakdown from the difference between flux and intake. The leucine intake as a component of the nutrient solution was the same in all the animals.

The fractional muscle protein synthetic rate was derived from the equation of Garlick et al.

$$SB/Si = \frac{\lambda i}{(\lambda i - ks)} \cdot \frac{(1 - e^{-ks.t})}{(1 - e^{-\lambda i.t})} - \frac{ks}{(\lambda i - ks)}$$

where SB is the specific radioactivity of leucine in the sulphosalicylic precipitated proteins and Si is the specific radioactivity of plasma ketoisocaproate obtained at the end of the infusion, both in dpm/μmol; λi is the rate constant for the rise in specific radioactivity of the precursor in days $^{-1}$; and K_s was the fraction of protein mass renewed each day in %/day. Because ketoisocaproate is generated in skeletal muscle from the deamination of leucine, its specific radioactivity represents the specific radioactivity of leucine in the muscle intracellular pool where leucine is transaminated.

Statistical Analysis

Data is presented as mean ± SEM for each group of 7 rats and were analyzed using an IBM 370/CMS-VSI computer system with the BMDP statistical package (Regents of the University of California, Los Angeles, CA). The groups of animals were compared by one-way analysis of variance and student's t test (two-tailed). Student's t test among the different groups was performed only when ANOVA test reached a 95% confidence level.

Results

The body weights before nutrient administration and the calories and amino acid intakes during the study period are summerized in Table 3.

Table 3

Initial Body Weight end Actual Dietary Intake During Feedings

GROUP	I	II	III	IV	V
Treatment: Base Solution + additional calories as:	---	Dextrose	LCT	MCT	Structured Lipid
N	7	7	7	7	7
Body Weight, g (Initial)	246±4	246±7	238±5	245±4	238±4
Pre-TPN Body Weight, g	238±5	238±5	233±6	240±6	231±6
Actual Calorie Intake, kcals/ kg.day	192±4	292±7**	290±8**	281±4**	306±7**
Nitrogen Intake g/kg.day	1.74±0.04	1.77±.04	1.75±0.05	1.70±0.03	1.86±0.04

Data expressed aa mean ± SEM: **p <0.01 vs group I

Thera waa no difference in body weight emong the five groups at the time of venous cannulation and one day following burn injury when meintained with only saline solutions.

Figure 1 ahows the percantage of body weight change after three days of diffarent nutritional support. The animals which received additionel calories as dextrose, soybean oil emulsion or atructured lipid emulsion gained weight significently, whereas those receiving medium chain triglyceride emulsiona (IV) lost weight aimilar to the hypocaloric feeding group (I).

The cumulative nitrogen balance during the parenteral infusion (Figure 2) did not show statistical differences among the groups. However, only those animals which received the additionel 100 kcals/kg BW · day were in positive nitrogen balence and in rats given the structured lipid emulsion, the belance was aignificantly positiva ($p<0.05$).

Serum glucose, β-hydroxybutyrate and insulin levels (Table 4) were different in rats given various diets. The lipid emulsions increased serum glucose and β-hydroxybutyrate concentrations compared with animals which received ell of their nonprotein calories es dextrose. Serum inaulin levels were clearly higher in those rats with increased dextrose intake (II) as well as animals given the medium chain triglycerlde emulsion (IV).

Table 4

Serum Substtrates and Insulin Concentrations

GROUP	I	II	III	IV	V
TPN + additional calories as:	——	Dextrose	LCT	MCT	Structured Lipid
Glucose (mg/dL)	121.0 ± 4.0	121.0 ± 7.2	180.6* ± 22.2	147.3 ± 15.7	161.3** ± 12.6
β-Hydroxybutyrate (mmol/L)	0.075 ± 0.02	0.051 ± 0.01	0.101[t] ± 0.02	0.257*[t] ± 0.08	0.123[t] ± 0.03
Lactate (mmol/L)	4.52 ± 0.51	4.48 ± 0.30	4.60 ± 0.31	4.49 ± 0.49	4.30 ± 0.34
Insulin (μU/ml)	22.6 ± 2.2	31.6** ± 1.6	21.3 ± 2.5	29.5 ± 2.5	22.6 ± 1.5

Dete expressed as mean ± SEM; **p < 0.05 and ** p < 0.01 vs group (Student's t test)
[t]p < 0.05 versus group II (Student's t test)
Liver weight and the percentage of protein were similar among the five groups (Table 5).

Table 5

Liver Protein Content and Serum Albumin Concentrations

GROUP	I	II	III	IV	V
TPN + additional calories as:	---	Dextrose	LCT	MCT	Structured Lipid
Liver weight (g/kg BW)	42.3 ± 2.3	48.3 ± 1.9	51.9 ± 3.7	50.2 ± 2.3	49.8 ± 3.5
Liver % protein (%)	16.2 ± 0.6	15.8 ± 0.3	15.7 ± 0.4	15.5 ± 0.2	16.5 ± 0.5
Liver Nitrogen (g/kg BW)	1.09 ± 0.04	1.21* ± 0.04	1.29* ± 0.07	1.22 ± 0.05	1.30* ± 0.06
Serum Albumin (g/dl)	2.94 ± 0.11	3.17 ± 0.09	3.11 ± 0.26	3.40** ± 0.07	4.06** ± 0.17

Data expressed as mean ± SEM; *p < 0.05 and ** p < 0.01 vs group (Student's t test)

Nevertheless, rats receiving additional dextrose, soybean oil or structured lipid emulsions showed increased nitrogen content in the liver. Serum albumin was markedly better in the groups infused with medium chain triglycerides (IV, V). The group with the structured lipid emulsion presented an albumin concentration 38% higher than the hypocaloric fed group (I).

Plasma amino acid concentrations are given in Table 6. Again, the animals which received either the medium chain or structured lipid emulsions had a significant reduction in branched chain amino acids without changes in the total amino acid concentrations.

Table 6

Plasma Amino Acid Concentrations

(nmol/L)	TAU	ASP	THR	SER	GLN	GLY	ALA	VAL	ISO	LEU	TYR	PHE	TAA	BCAA
Group I	346 ±21	114 ±64	621 ±56	490 ±42	134 ±3	1038 ±162	942 ±126	731 ±30	290 ±27	402 ±35	46 ±2	165 ±16	5319 ±445	1422 ±93
Group II	419 ±56	54 ±5	770 ±54	571 ±37	130 ±5	984 ±61	990 ±50	715 ±22	269 ±10	347 ±10	37 ±5	139 ±5	5425 ±209	1331 ±37
Group III	299 ±64	43 ±6	749 ±51	614* ±32	96** ±6	1125 ±145	968 ±98	624 ±109	301 ±38	389 ±48	46 ±8	174 ±16	5458 ±534	1314 ±181
Group IV	379 ±58	50 ±6	616 ±51	482 ±29	80 ±2	824 ±83	968 ±35	550** ±38	205* ±16	286** ±16	38 ±3	152 ±8	4632 ±266	1042** ±70
Group V	501 ±50	43 ±5	757 ±40	661** ±30	114 ±11	1229 ±139	890 ±51	478** ±26	174** ±8	216** ±13	37 ±6	147 ±6	5245 ±179	870** ±45

* p<0.05 vs Group I

** p<0.01 vs Group I

TAU=taurine, ASP=aspartate, THR=threonine, SER=serine, GLN=glutamine, GLY=glycine, ALA=alanine, VAL=valine, ISO=isoleucine, LEU=leucine, TYR=tyrosine, PHE=phenylalanine, TAA=total amino acids, BCAA=branched chain amino acids

The changes in leucine kinetics are summarized in Table 7. During a constant amino acid infusion administering leucine at 62.2 ± 0.65 µmols/100 g body weight · h, whole body leucine appearance, incorporation into and release from protein did not show major changes. However, leucine oxidation was significantly reduced in the rats which received additional calories as a structured lipid emulsion (V). This group also was the only one that showed an improvement in net leucine balance (difference between incorporation into and release from protein) compared with the control group (I).

Protein fractional synthetic rate in the gastrocnemius muscle (Table 7) changed only minimally with the addition of dextrose or different lipid emulsions over the hypocaloric parenteral feeding in these burned rats.

Table 7

Whole Body Leucine Kinetics and Muscle Protein Fractional Synthesis Rate (FSR)

	Flux	Oxidation	Incorporation Into Protein	Release from Protein	Balance	Muscle Protein FSR
			u mols leucine/ 100/g BW · BW			% day
I	93.6	30.0	63.6	29.3	+ 34.2	8.4
	±	±	±	±	±	±
	7.7	3.3	5.0	7.1	3.2	0.8
II	84.2	22.5	61.7	22.1	+ 39.5	10.3
	±	±	±	±	±	±
	3.8	1.3	3.8	3.7	1.8	0.7
III	99.3	23.6	75.7	37.8	+ 38.0	8.9
	±	±	±	±	±	±
	6.8	1.9	5.8	6.8	1.9	0.9
IV	83.0	24.7	58.3	21.1	+ 37.2	9.5
	±	±	±	±	±	±
	5.3	7.3	3.4	4.9	2.2	0.8
V	81.7	17.7**	64.1	20.6	+ 43.5*	9.4
	±	±	±	±	±	±
	4.6	1.2	4.2	4.7	1.3	0.5

Data expressed as mean ± SEM; *p<0.05 and ** p<0.01 versus Group I (Student's t test)

Effects on RES

(guinea pig studies)

Increased lipid rather than carbohydrate administration has been recommended for traumatized patients because it decreases CO_2 production, is isotonic, and does not compromised individuals. The associated hyperinsulin response to high carbohydrate intakes has also been implicated as an indication of the Kwashioorkor-like malnutrition which results in reduced hepatic secretory protein concentrations. However, results also suggest that high lipid administration may increase the risk of infections by impairing the animal's RES. The standard technique for producing fibronectin deficiency and reticuloendothelial system blockade in experimental animals is to administer long chain fatty acid triglyceride emulsions. Presently available IV fat emulsions caution against using the emulsions for more than 60% of the patient's total calories.

To evaluate the potential blocking of the RES during lipid administration, burned guinea pigs were parenterally fed isocaloric, isonitrogenous diets for three days in which 50% or 75% of the non-protein calories were administered as a long chain triglyceride (LCT), medium chain triglyceride emulsion (MCT) or the synthetic triglyceride (Captex 810 B) described above. The guinea pigs received a total of 300 Kcals/kg body weight . day, and 12.5 g amino acid/kg body weight . day for three days following a 25% full-thickness burn. The diets were intravenously administered through a central venous catheter and differed only in the source of lipid administered as well as the ratio of lipid to glucose non-protein calories. On the last day, the uptake of ^{59}Fe-Pseudomonas aeruginosa by the RES was measured. 1 x 10^6 bacteria/gram of body waight were incubated for 48 hours with 50 - 100 µU of 59 Fe-citrate. The radiolabeled bacteria were washed and intravenously injacted into tha guinea pigs to produce an initial blood bacteremia of 1 x 10^7 c.f.u./ml of blood. After 60 minutes, the guinea pigs were exsangulnated and the quantity of radiolabeled bacteria sequestered on the organs of the reticuloendothelial system were determined. The resulta obtained comparing the LCT with the MCT are shown in Table 8. The results obtained comparing the LCT with the Ceptex 810 b are shown in Table 9.

Table 8

(LCT vs. MCT)

(% Uptake) X±S.D.	50% Lipid Unburned LCT	50% Lipid Burned LCT	50% Lipid Burned MCT	75% Lipid Unburned LCT	75% Lipid Burned LCT	75% Lipid Burned MCT
Liver	46.5 ± 2.8	47.5 ± 4.6	44.0 ± 6.4	45.2 ± 5.2	28.0 ± 7.7*	43.5 ± 6.2
Lung	1.9 ± 0.5	1.6 ± 0.2	2.0 ± 0.6	2.5 ± 0.9	6.8 ± 5.9*	2.4 ± 0.7

*p < vs MCT.

These results suggest that high Lipid administration as LCT following a thermal injury reduce the uptake of bacteria in the liver and increase localization of bacteria in the lungs. These defects are not seen when the source of Lipid is MCT. Previous studies with LCT in hypocaloric regimens have shown similar defects in the RES when only Lipid was administered. It can be concluded that RES function is dependent not solely on the quantity of Lipid administered but also the type of Lipid infused.

Table 9

(LCT vs. Synthetic triglyceride - [SYN.T])

(% Uptake) X±S.D.	50% Lipid Unburned LCT	50% Lipid Burned LCT	50% Lipid Burned SYN.T.	75% Lipid Unburned LCT	75% Lipid Burned LCT	75% Lipid Burned SYN.T.
Liver	46.5 ± 2.8	47.5 ± 4.6	44.0 ± 6.4	45.2 ± 5.2	28.0 ± 7.7*	41.5 ± 3.9
Lung	1.9 ± 0.5	1.6 ± 0.2	2.0 ± 0.6	2.5 ± 0.9	6.8 ± 5.9*	2.79± 1.4

* $p < 0.05$ vs MCT.

Although both the MCT end the SYN.T. (structured lipid) could be administered in amounts greater than 60% of the caloric requirements of the hypercatebolic guinea pigs, it was found that the use of the MCT at the 75% celoric level resulted in a significantly higher rate of complications and mortelity than the SYN.T. given at the aame 75% level, or the LCT or Dextrose combinetions in protein-depleted guinea pigs. These results are summarized in Table 10.

The studies were identicel to those previously described except thet the guinea pigs were protein-depleted by consuming a 2% casain diet for two weeks prior to the thermel injury.

Table 10

(Complicetions*/Mortelity)

Combination	No. Animals	Complications	Mortality
AA + LCT	12	2	1
AA + Dextrose	13	4	0
AA + MCT	11	8	5
AA + SYN.T.	12	4	1

* MCT Complications: Acute Renal Failure - 1
Pulmon/Cardiac Failure - 4
Rectal Prolapse - 2

LEGENDS TO FIGURES

FIGURE 1 - Changes in body weight following a burn in rats receiving different total parenteral nutrition regimens.

Changes in body weight reflect the differences between the first day following the burn when the animal was only infused with saline and the end of the study at sacrifice.

FIGURE 2 - Daily cumulative nitrogen balance

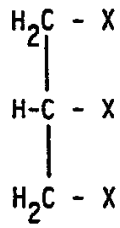
During the first day following the burn injury all of the animals were infused with only physiologic saline. By the end of the fourth day, all of the animals receiving additional calories were in positive balance but only in rats given the structured lipid emulsion were the differences from zero statistically significant. Values represent the mean and standard error for each group.

Claims

1. A parenterally administrable product comprising an emulsion of lipids in combination with a carbohydrate and amino acid source, said product being capable of safely enhancing protein anebolism in e hypercatabolic mammal, characterized in that the emulsion of lipids on hydrolysis yields both long chain fatty acids and medium chain fatty ecids.

2. A product according to claim 1, characterized in that the said product contains an amount of lipids capable of providing more than 60% of the total caloric requirements of the hypercatabolic mammal without impairment of the mammal's reticuloendothelial system.

3. A product according to claim 1 or 2, characterized in that the lipids comprise a mixture of synthetic triglycerides having the formula



where X represents long and medium fatty acid residues, with at least ona of aach being present.

4. A product eccording to any of claims 1 to 3, charecterized in that a long chein fatty acid residue is an essential fatty ecid residue.

5. A product eccording to any of claims 1 to 4, charecterized in thet a medium chain fatty acid residue is selected from C_8, C_{10} and C_{12} fatty ecid residuas.

6. A product according to claim 1 or 2, characterized in thet the lipide comprise a physicel mixtura of long chain triglycerides and medium chein triglyceridas.

7. A product according to any of cleime 1 to 6, charactarized in that tha lipids, on hydrolysis, ylald 20 to 80% of long chein fetty ecids and 80 to 20% of medium chain fatty acids.

8. A process for the preparation of a parantally administrabla product comprising an amulsion of lipids in combinetion with a cerbohydrete end amino ecid sourca, eeid product baing cepable of sefaly enhancing protein anaboliem in a hypercetebolic mammel, cherectarizad in that en emulsion of lipids, which on hydrolysis yields both long cheln fatty ecids and medium chein fetty acids, is admixad with e cerbohydrete end amino acid source.

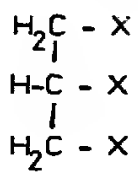
9. A process according to claim 8, charactarizad in thet the lipid componant is es specified in claims 3-7.

Patentansprüche

1. Ein paranterel verebreichbares Produkt, das eine Emulsion von Lipidan in Kombination mit einer Kohlenhydrat- und Aminosäurequelle umfeßt; besagtes Produkt ist fähig den Proteinenebolismus in einem hyperkatebolischen Säugetier sicher zu erhöhen und ist dadurch gekennzeichnat, daß dia Emulsion von Lipiden bei der Hydrolyse lengkettige Fettsäuren und Fettsäuren mit mittlerer Länge liefert.

2. Ein Produkt gemäß Anspruch 1 iet dadurch gekennzeichnet, daß das besagte Produkt einen Lipidanteil enthält der fähig ist, mehr als 60% des Gesamtkalorienbedarfs des hyperkatabolischen Säugetiers ohne Beeinträchtigung des Säugetierreticuloendothelialsystems zu liefern.

3. Ein Produkt gemäß Anspruch 1 oder 2, das dadurch gekennzeichnet ist, daß die Lipide eine Mischung von synthetischen Triglyceriden mit der Formel



umfaßt, worin X einen langen oder mittellangen Fettsäurerest darstellt, wobei zumindest einer der beiden Reste vorhanden ist.

4. Ein Produkt gemäß Anspruch 1 bis 3, ist dadurch gekennzeichnet, daß ein langkettiger Fettsäurerest ein essentieller Fettsäurerest ist.

5. Ein Produkt gemäß Anspruch 1 bis 4 ist dadurch gekennzeichnet, daß ein mittellanger Fettsäurerest aus C_8, C_{10} und C_{12} Fettsäureresten ausgewählt wird.

6. Ein Produkt gemäß Anspruch 1 oder 2 ist dadurch gekennzeichnet, daß die Lipide eine physikalische Mischung aus langkettigen Triglyceriden und Triglyceriden mit mittlerer Kettenlänge umfassen.

7. Ein Produkt gemäß Anspruch 1 bis 6 ist dadurch gekennzeichnet, daß die Lipide bei Hydrolyse 20 bis 80% langkettige Fettsäuren und 80 bis 20% Fettsäuren mit mittlerer Kettenlänge liefern.

8. Ein Verfahren zur Herstellung eines parenteral verabreichbaren Produktas umfaßt eine Emulsion von Lipiden in Kombination mit einer Kohlenhydrat- und Aminosäurequelle; besagtes Produkt ist fähig den Proteinanabolismus in einem hyperkatabolischen Säugetier sicher zu erhöhen und ist dadurch gekennzeichnet, daß die Emulsion von Lipiden bei der Hydrolyse lengkettige Fettsäuren und Fettsäuren mit mittlerer Kettenlänge liefert; eine Kohlenhydrat- und Aminosäurequelle wird zugemischt.

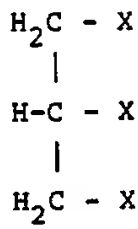
9. Ein Verfahren gemäß Anspruch 8 ist dadurch gekennzeichnet, daß die Lipidkomponente wie in Anspruch 3 - 7 spezifiziert ist.

Revendications

1. Produit, administrable per voie parentérale, comprenant une émulsion de lipides en combinaison avec una source da glucides et d'aminoacides, ladit produit étant capable d'amplifier sûrement l'anabolisma des protéines chez un mammifère hypercatabolique, produit caractérisé an ca qua l'émulsion de lipidas donna par hydrolysa à la fois des acidas gras à longue chaîne at des acides gras à chaîne de longueur moyenne.

2. Produit salon la revandication 1, caractérisé en ce qua ladit produit contiant una quantité da lipidas capable de fournir plus de 60 % des exigences caloriques totales du mammifère hyparcataboliqua sans nuira au système réticuloandothélial du mammifère.

3. Produit selon la revendication 1 ou 2, caractérisé en ca qua les lipides comprannant un mélanga da triglycérides synthétiques répondant à la formule



dans laquelle X représente des restes d'acide gras longs et moyens, au moins un de chaque étant présent

4. Produit selon l'une quelconque des revendications 1 à 3, caractérisé en ce qu'un reste d'acide gras à longue chaîne est un reste d'acide gras essentiel.

5. Produit selon l'une quelconque des revendications 1 à 4, caractérisé en ce qu'un reste d'acide gras à chaîne moyenne est choisi parmi les restes d'acide gras en C_8, C_{10} et C_{12}.

6. Produit selon la revendication 1 ou 2, caractérisé en ce que les lipides comprennent un mélange physique de triglycérides à longue chaîne et de triglycérides à chaîne moyenne.

7. Produit selon l'une quelconque des revendications 1 à 6, cerectérisé en ce que les lipides donnent, par hydrolyse, 20 à 80 % d'acides gras à longue chaîne et 80 à 20 % d'acides gras à chaîne de longueur moyenne.

8. Procédé pour la préparation d'un produit administrable par voie parentérale, comprenant une émulsion de lipides en combinaison avec une source de glycides et d'aminoacides, ledit produit étant capable d'augmenter sûrement l'anabolisme des protéines chez un mammifère hypercatabolique, procédé caractérisé en ce qu'on mélange une émulsion de lipides qui donne par hydrolyse à la fois des acides gras à longue chaîne et des acides gras à chaîne de longueur moyenne, avec une source de glucides et d'aminoacides.

9. Procédé selon la revendication 8, caractérisé en ce que le composant lipidique est tel que spécifié aux revendications 3-7.

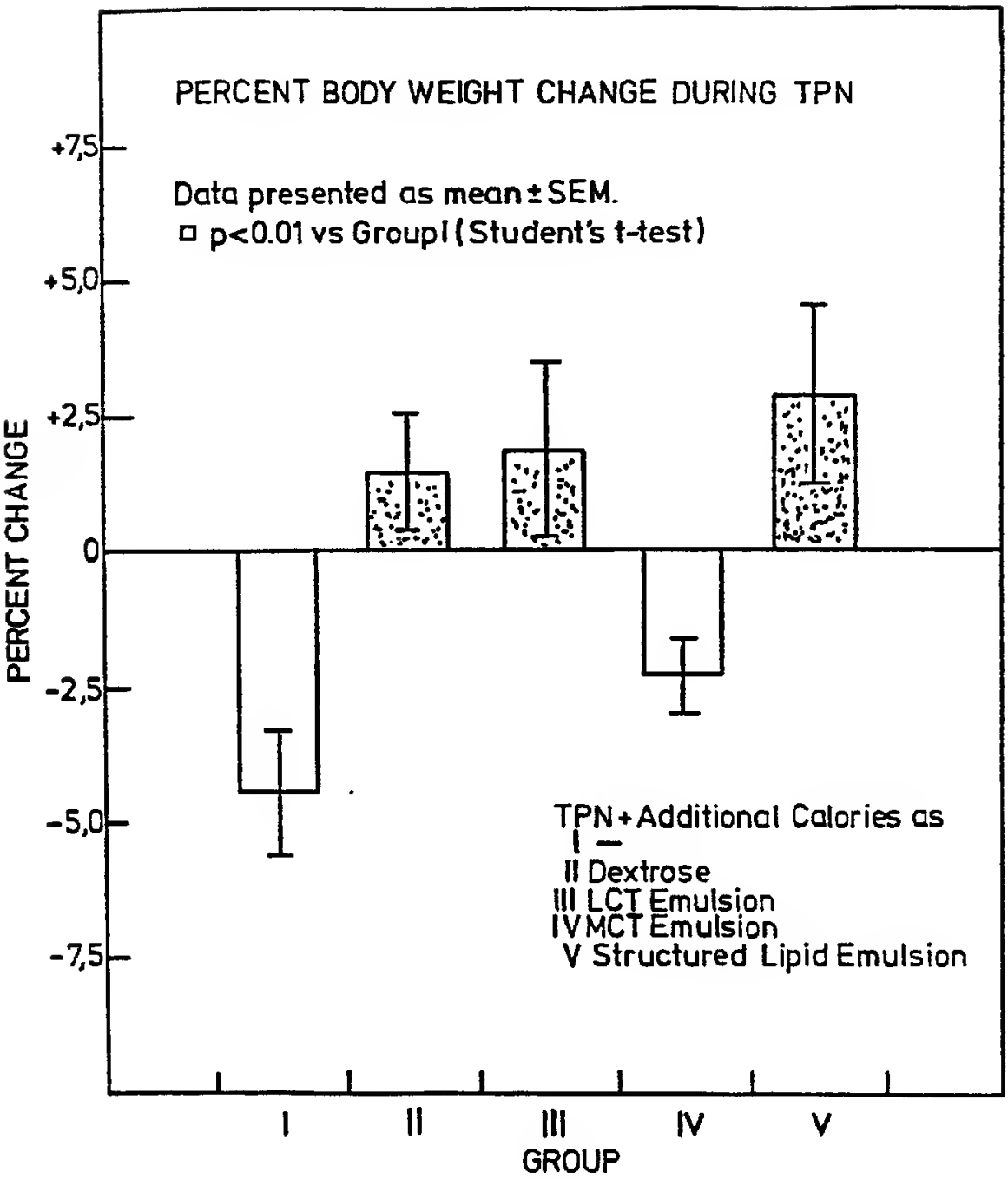
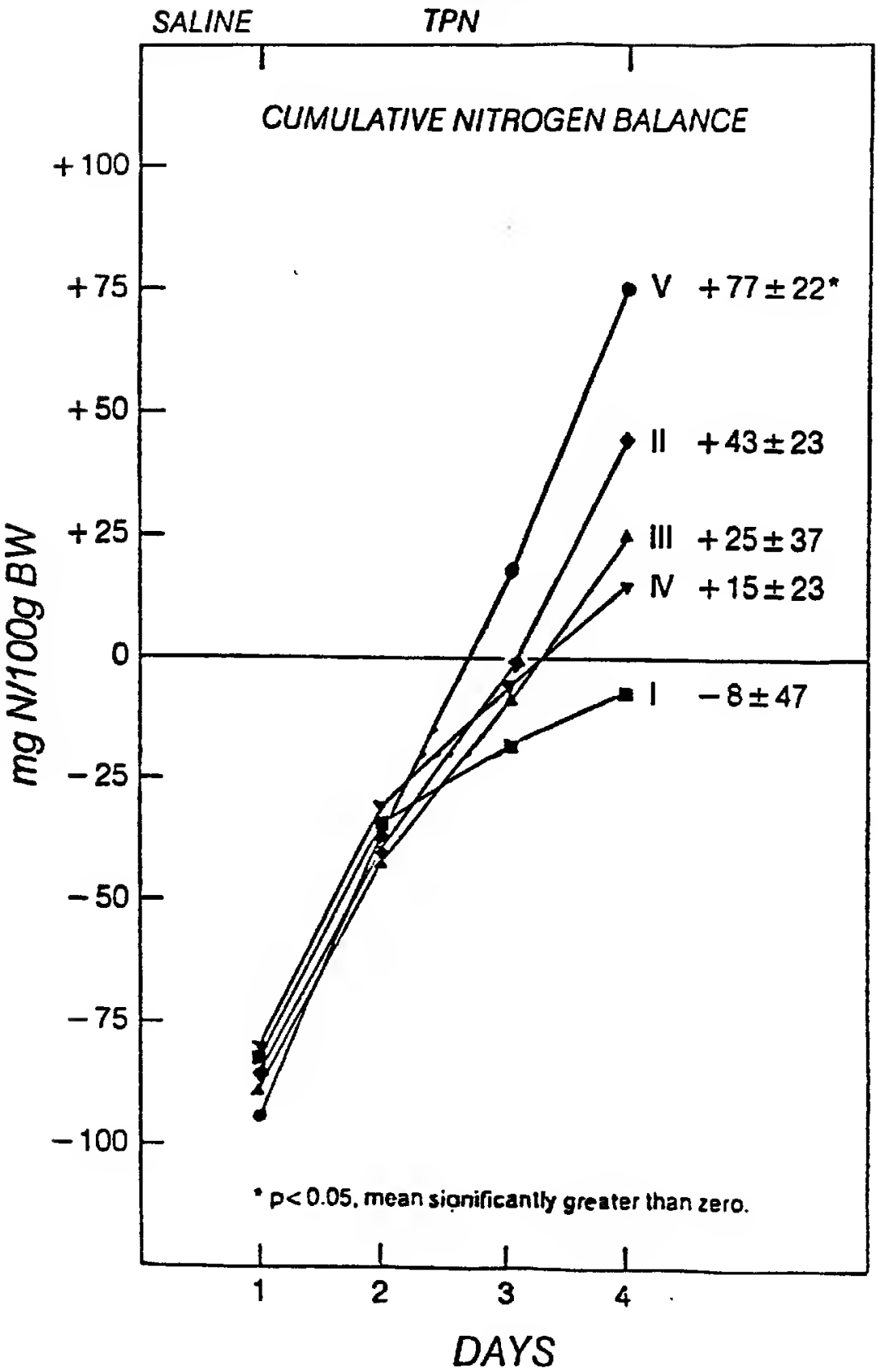

PERCENT BODY WEIGHT CHANGE DURING TPN
Data presented as mean ± SEM.
□ p<0.01 vs Group I (Student's t-test)
+7,5
+5,0
+2,5
0
-2,5
-5,0
-7,5
PERCENT CHANGE
TPN + Additional Calories as
II Dextrose
III LCT Emulsion
IV MCT Emulsion
V Structured Lipid Emulsion
I
II
III
IV
V
GROUP

FIG. 1


SALINE
TPN
CUMULATIVE NITROGEN BALANCE
+100
+75
+50
+25
0
−25
−50
−75
−100
mg N/100g BW
V +77±22*
II +43±23
III +25±37
IV +15±23
I −8±47
* p< 0.05, mean significantly greater than zero.
1
2
3
4
DAYS